

under Obviousness-Type Double Patenting over Claims 1 and 12 of co-pending Application Serial No. 08/321,552. Claims 1-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al., J. Biol. Chem., 26(22) 14338-42 (1991) (Wu), in view of Kornguth et al., U.S. Patent 5,230,883 (Kornguth). Applicant takes note of the Examiner's withdrawal of the previous Statutory-Type Double Patenting rejection of Claims 1-4, 6-10, 12-13, 16 and 22. Favorable consideration of the claims in view of the following comments is respectfully requested.

#### The Invention

The present invention teaches compositions and methods using delivery vehicles that can specifically deliver physiological agents. The delivery vehicles generally comprise four elements: (1) a first polymeric molecule having a net positive or net negative charge; (2) at least a second polymeric molecule having a net charge opposite to the first polymeric molecule; (3) a cell targeting moiety attached to the second polymeric molecule (or a third polymeric molecule similar to the second polymeric molecule); and (4) a physiological agent attached to the first or second polymeric molecule (or a third polymeric molecule similar to the second polymeric molecule). The physiological agent can be a therapeutic agent, such as a drug, hormone, enzyme, protein or peptide, anti-cancer agent, etc., or a contrasting agent, such as magnetic resonance imaging contrasting agents, radioisotope contrast agents, gamma emitter contrast agents, positron emitter contrast agents, beta emitter contrast agents and optical contrast agents, including fluorescent contrast agents. The Applicants submit that none of the prior art references, taken alone or in combination, teach or suggest the present invention.

#### Obviousness-Type Double Patenting

Claims 1-3, 10-13, 16-19, 21 and 22 stand rejected under Obviousness-Type Double Patenting over Claims 1 and 12 of commonly assigned U.S. Patent No.6,232,295. A Terminal Disclaimer is filed herewith to obviate this rejection.

#### 35 U.S.C. 103(a)

Claims 1-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wu, in view of Kornguth. Applicants vigorously traverse this rejection.

Wu teaches a method for the delivery of a foreign gene to hepatocytes. The method makes use of complexes with three components: (1) a DNA molecule; (2) a polycation; and (3) an asiaglycoprotein molecule. In this method an asiaglycoprotein molecule is first chemically coupled to a polycation, such as poly-lysine. The asiaglycoprotein/polycation couple is then mixed with the DNA to be delivered. The negatively charged backbone of the DNA binds to the positively charged polycation portion of the asiaglycoprotein/polycation couple. After administration, the complex is specifically taken up by hepatocytes via unique receptors that recognize the asiaglycoprotein portion of the asiaglycoprotein/polycation couple and internalize the entire complex.

Kornguth discloses methods for imaging and treatment of tumors having net negative charge. The methods make use of complexes with three components: (1) polylysine molecules; (2) Linking agents; and (3) imaging or chemotherapeutic agents. In these methods a limited number of the lysyl residues of the polylysine molecules are initially modified by attachment of a linking agent, such as diethylene triamine pentacetic acid dianhydride (DTPA). After the DTPA (or other linking groups) attachment to the polylysine molecules, imaging or chemotherapeutic agents may be introduced and chelated. The final complex may then be administered and will bind negatively charged tumors via the unmodified lysyl residues that still retain their positive charge.

As stated in M.P.E.P. § 2142, a *prima facie* case of obviousness requires three basic criteria to be met. First, there must be some suggestion or motivation to combine the various references' teachings. Second, there must be a reasonable expectation of success. Finally, the references, taken alone or in combination, must teach or suggest all the claim language.

The Applicants continue to maintain that there is no motivation to combine the teachings of Wu and Kornguth, as such a combination would render the invention of Kornguth incapable of meeting its objectives. In such a combination the positive charge necessary for binding negatively charged tumor cells, as taught by Kornguth, would be neutralized if the positive polylysine was used as a carrier as described in Wu. As outlined in the M.P.E.P § 2143.01:

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.

See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

Additionally, such a combination would materially change the way in which Kornguth's invention functions. The combination would require a molecule previously used for targeting to be used as a carrier, thus requiring a new and undisclosed targeting molecule. It is well settled that if the combination of references would change the principle of operation of the prior art then it is impermissible to use them to establish prima facie obviousness, as stated in M.P.E.P § 2143.01

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious.

See *In re Ratti*, 123 USPQ 349 (CCPA 1959).

The Examiner has attempted to rebut the Applicants' argument that there is no motivation to combine Wu and Kornguth by asserting the following:

Motivation for combining the references is based upon the critical teachings of Kornguth et al. in the context of Wu et al wherein each element of the Applicant's invention with the exception of an imaging agent is disclosed. However, since it is recognized in the art that polylysine is useful as a carrier molecule of components of interest including cell targeting molecules and contrast agents, one would be motivated to use polylysine conjugates to deliver nucleic acids as set forth in Applicant's claims 2-3 and 8 for deliver of imaging agents.

This line of argumentation ignores that Kornguth employs polylysine for the targeting of contrast or chemotherapeutic agents to negatively charged tumors, not as a carrier. As pointed out above and in our previous response of September 11, 2000, if one were to use polylysine as a carrier molecule, the aims of Kornguth, namely to target contrast or chemotherapeutic agents to negatively charged tumor cells, would be thwarted. Accordingly, there cannot be any motivation to combine the teaching of Kornguth with Wu.

Additionally, The Examiner's attention is respectfully drawn to In re Lee, 61 USPQ2d 1430 (CA FC 2002). In this case, an examiner rejected claims under 35 U.S.C. §103 and upon appeal to the Board of Patent Appeals and Interferences the Board stated that the required motivation to combine prior art references "may be made from common knowledge and common sense of a person of ordinary skill in the art without any specific hint or suggestion in a particular reference." *Id* at 1432. The Federal Circuit rejected this analysis as "legal error and arbitrary agency action." *Id* at 1434. The Federal Circuit then made clear that the Board's finding must extend to all material facts and must be documented on the record, lest the "haze of so-called expertise" acquire insulation from accountability. "Common knowledge" and "common sense", even if assumed to derived from the agency's expertise, do not substitute for authority when the law requires authority." (citing In re Zurko, 59 USPQ2d 1693 (CA FC 2001); see Lee, 1434-1435).

By arguing that it was common knowledge that polylysine could be used as a carrier, and that this common knowledge would motivate someone with ordinary skill in the art to combine the teachings of Kornguth with Wu, the Examiner has essentially used impermissible hindsight and "common sense" to conclude that the combination of these two references leads to the claimed invention. This is legally impermissible under the Federal Circuit's analysis.

Furthermore, Applicants would like to remind the Examiner that it is impermissible to pick and choose aspects of a prior art reference while ignoring other aspects of the reference that clearly teach away from the instant invention. As outlined in the M.P.E.P. §2141.02:

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.

See *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983); *cert. denied*, 469 U.S. 851 (1984).

Furthermore, in *In re Wesslau*, the Court of Customs and Patent Appeals held:

It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given

position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

See *In re Wesslau*, 147 USPQ 391, 393 (CCPA 1965).

In response to the Examiner's query in the March 10, 2000 Office Action, the applicants respectfully wish to point out how Kornguth teaches away from the present invention and why that fact does not contradict the present disclosure. As stated previously, Kornguth teaches that a high positive charge is necessary to target its complexes to negatively charged tumors. See Kornguth at 2:6-11; 2:62-65; and 3:30-43. Therefore attempting to deliver a nucleic acid, as proposed by the Examiner, is impossible under Kornguth as the nucleic acid would neutralize the positive charge of the polylysine. This is not contradictory to the present invention because the present invention has no such limitation on charge, due to its separate targeting moiety. DNA may therefore be bound by the polylysine of the instant invention without any adverse effects on targeting, something impossible under the teaching of Kornguth. Thus, again, there cannot be any motivation to combine the teaching of Kornguth with Wu to render the instant invention *prima facie* obvious, since Kornguth actually teaches away from the present invention.

Based on the foregoing arguments, Applicants respectfully submit that the rejection under §103 is improper as the Examiner has not established a *prima facie* conclusion of obviousness against Claims 1-22. Accordingly, Applicants respectfully request that the rejection be withdrawn.

### Conclusion

Applicants respectfully submit that the pending claims are in condition for allowance. An early notification to that effect is respectfully requested. If a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney. This paper is filed under 37 C.F.R. section 1.34(a).

Respectfully submitted,  
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